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SEARCH REQUEST FORM

Requester's Full Name: JANE ZARA Examiner #: 77512 Date: 3-25-05
Art Unit: 1635 Phone Number: 2-0765 Serial Number: 09/355,254
Location (Bldg/Room#): 2D28 (Mailbox #): 2C18 Results Format Preferred (circle): PAPER DISK

To ensure an efficient and quality search, please attach a copy of the cover sheet, claims, and abstract or fill out the following:

Title of Invention: Pharm Comp.

Inventors (please provide full names): H. Wagner et al.

Earliest Priority Date: (B) 2-22-00

Search Topic:

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc., if known.

For Sequence Searches Only Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.

Please Search Seq ID Nos 8-14,
16, 17, 19-23

- Size limit to 60 ~~100~~ NT's.

- No Size limit.

Please Search Interference
& regular Data Base.

Set	Items	Description
S1	3910	ANTIGEN? (S) CPG
S2	22714200	1 NOT PD=>1998
S3	2601	S1 NOT PD>1998
S4	1099	RD (unique items)
S5	316	S4 AND (IMMUNOMOD? OR TH1 OR TH2)
S6	94	S5 AND PHARMAC?
S7	94	S6 NOT PD>1997
S8	33	S7 AND (POLYNUCLEOTIDE? OR OLIGONUCLEOTIDE?)
S9	0	S5 AND T(TRANSCRIPTION (W) FACTOR?)
S10	6	S5 AND (TRANSCRIPTION (5N) FACTOR?)
S11	169	S1 AND (TRANSCRIPTION (6N) FACTOR?)
S12	96	RD (unique items)
S13	1218	S1 AND (IMMUNOMOD? OR TH1 OR TH2)
S14	16	S12 AND (IMMUNOMOD? OR TH1 OR TH2)

>>>KWIC option is not available in file(s): 399

14/3,K/1 (Item 1 from file: 5)
 DIALOG(R)File 5:Biosis Previews(R)
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0014351177 BIOSIS NO.: 200300308666

Divergent synthetic nucleotide motif recognition pattern: Design and development of potent **immunomodulatory** oligodeoxyribonucleotide agents with distinct cytokine induction profiles.

AUTHOR: Kandimalla Ekambar R; Bhagat Lakshmi; Wang Daqing; Yu Dong; Zhu Fu-Gang; Tang Jimmy; Wang Hui; Huang Ping; Zhang Ruiwen; Agrawal Sudhir (Reprint)

AUTHOR ADDRESS: Hybridon, Inc., 345 Vassar Street, Cambridge, MA, 02139, USA**USA

AUTHOR E-MAIL ADDRESS: sagrawal@hybridon.com

JOURNAL: Nucleic Acids Research 31 (9): p2393-2400 May 1, 2003 2003

MEDIUM: print

ISSN: 0305-1048 (ISSN print)

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

Divergent synthetic nucleotide motif recognition pattern: Design and development of potent **immunomodulatory** oligodeoxyribonucleotide agents with distinct cytokine induction profiles.

ABSTRACT: Unmethylated **CpG** dinucleotides present within certain specific sequence contexts in bacterial and synthetic DNA stimulate innate immune responses and induce cytokine secretion. Recently, we showed that **CpG** DNAs containing two 5'-ends, immunomers, are more potent in both regards. In this study, we show that an immunomer containing a synthetic CpR motif (R=2'-deoxy-7-deazaguanosine) is a potent immunostimulatory agent. However, the profile of cytokine induction is different from that with immunomers containing a natural *****CpG***** motif. In general, a CpR immunomer induced higher interleukin (IL)-12 and lower IL-6 secretion. Compared with conventional *****CpG***** DNAs, both types of immunomers showed a rapid and enhanced activation of the *****transcription***** *****factor***** NF-kappaB in J774 cells. NF-kappaB activation by **CpG** DNA corresponded to degradation of IkappaBalpha in J774 cells. All three immunostimulatory oligonucleotides activated the p38 mitogen-activated protein kinase pathway as expected. Immunomers containing **CpG** and CpR motifs showed potent reversal of the **antigen-induced Th2** immune response towards a **Th1** type in *****antigen***** -sensitized mouse spleen cell cultures. Immunomers containing a CpR motif showed significant antitumor activity in nude mice bearing MCF-7 human breast cancer and U87MG...

14/3,K/2 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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13239875 Genuine Article#: 861BX Number References: 42
Title: Suppressive oligodeoxynucleotides inhibit **Th1** differentiation
by blocking IFN-gamma- and IL-12-mediated signaling
Author(s): Shiota H; Gursel M; Klinman DM (REPRINT)
Corporate Source: US FDA,Ctr Biol Evaluat & Res, Sect Retroviral
Immunol,Bldg 29A Room 3 D10/Bethesda//MD/20892 (REPRINT); US FDA,Ctr
Biol Evaluat & Res, Sect Retroviral Immunol,Bethesda//MD/20892(
Klinman@cber.fda.gov)
Journal: JOURNAL OF IMMUNOLOGY, 2004, V173, N8 (OCT 15), P5002-5007
ISSN: 0022-1767 Publication date: 20041015
Publisher: AMER ASSOC IMMUNOLOGISTS, 9650 ROCKVILLE PIKE, BETHESDA, MD
20814 USA
Language: English Document Type: ARTICLE (ABSTRACT AVAILABLE)

Title: Suppressive oligodeoxynucleotides inhibit **Th1** differentiation
by blocking IFN-gamma- and IL-12-mediated signaling
Abstract: Repetitive TTAGGG motifs present at high frequency in mammalian
telomeres can suppress *****Th1***** -mediated immune responses. Synthetic
oligonucleotides (ODN) containing TTAGGG motifs mimic this activity and
have proven effective in the prevention/ treatment of certain **Th1**
-dependent autoimmune diseases. This work explores the mechanism by
which suppressive ODN block the induction of *****Th1***** immunity.
Findings indicate that these ODN inhibit IFN-gamma-induced STAT1
phosphorylation and IL-12-induced STAT3 and STAT4 phosphorylation. As a
result, T-bet expression is reduced as is the maturation of naive
CD4(+) cells into *****Th1***** effectors. These changes indirectly support
the generation of *****Th2***** -dominated immune responses. Suppressive ODN
may thus represent a novel approach to influence the **Th1**:
*****Th2***** balance in vivo.

...Identifiers--T-CELL-CLONE; INDUCED IMMUNE ACTIVATION; STIMULATORY
CPG MOTIFS; BACTERIAL-DNA; TYROSINE PHOSPHORYLATION;
TRANSCRIPTION FACTOR; INDUCED ARTHRITIS; **ANTIGEN**;
INTERLEUKIN-12; LYMPHOCYTES

14/3,K/3 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE
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07916621 EMBASE No: 1999390085
Antisense strategies to inhibit restenosis
Lee M.; Simon A.D.; Stein C.A.; Rabbani L.E.
Dr. L.E. Rabbani, Department of Medicine, Columbia University, College of
Physicians and Surgeons, 630 West 168th Street, New York, NY 10032
United States
AUTHOR EMAIL: ler@columbia.edu
Antisense and Nucleic Acid Drug Development (ANTISENSE NUCLEIC ACID DRUG
DEV.) (United States) 1999, 9/5 (487-492)
CODEN: ANADF ISSN: 1087-2906
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 52

...in vitro SMC proliferation and migration. Moreover, PS
oligodeoxynucleotides targeted against the genes c-myb, c-myc, cdc2 kinase,
cdk2 kinase, and proliferating cell nuclear **antigen** (PCNA) when
delivered adventitiously or intraluminally inhibit in vivo neointimal

formation after balloon injury in both the rat carotid and porcine coronary artery models. The...

...manifest comparable in vivo inhibitory effects on neointimal formation in the rat carotid artery model of balloon injury. PS oligodeoxynucleotides also possess non-sequence-specific **immunomodulatory** effects, including the induction of interferon-gamma and the unmethylated **CpG** motif, which exhibits numerous *****immunomodulatory***** effects. Novel strategies to inhibit restenosis include the development of E2F transcription decoys that inhibit several cell cycle regulatory genes and diminish neointimal lesion formation...

DRUG DESCRIPTORS:

oligodeoxynucleotide phosphorothioate; protein kinase--endogenous compound --ec; cycline--endogenous compound--ec; oncoprotein--endogenous compound --ec; mitogenic agent; cytidine; chemoattractant; platelet derived growth **factor**; basic fibroblast growth **factor**; **transcription factor** e2f; protein bcl x--endogenous compound--ec

14/3,K/4 (Item 1 from file: 135)
DIALOG(R)File 135:NewsRx Weekly Reports
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0000069856 (USE FORMAT 7 OR 9 FOR FULLTEXT)
Novel DNA molecules are potent, selective immunoregulators
Immunotherapy Weekly, November 20, 2002, p.4

DOCUMENT TYPE: Editor's Choice LANGUAGE: English
RECORD TYPE: FULLTEXT
WORD COUNT: 438

The in vitro and in vivo research data show that these second-generation synthetic CpG **immunomodulators** have significantly increased metabolic stability as compared to the native compound, and induce higher secretion of disease fighting interleukin-12 (IL-12), with minimal induction...

...s scientists and their collaborators at the University of Alabama at Birmingham is a highly promising advance in the development of potent, specific and tolerable *****immunomodulatory***** molecules," said James B. Wyngaarden, MD, Hybridon. "There is a great demand in the medical community to use the body's immune system to fight...

...phosphorothioate backbone modification or poly(dG) structures that are commonly used, but have various limitations associated with them. The Hybridon molecules activate one of the **transcription factors**, NF-kB, that is responsible for upregulation of cytokine gene expression. However, by virtue of their design, they selectively induce higher IL-12 secretion with only minimal IL-6 secretion.

As a result of these properties, these novel **CpG** DNA molecules show potent antitumor activity in tumor xenograft models in nude mice. In addition, because of their ability to selectively induce IL-12 secretion...

...with vaccines and monoclonal antibodies for a number of other disease conditions, and as treatments for asthma and allergic conditions alone or in combination with *****antigens*****.

This article was prepared by Immunotherapy Weekly editors from staff and other reports.

14/3,K/5 (Item 1 from file: 144)
DIALOG(R)File 144:Pascal
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15365304 PASCAL No.: 02-0053185

ETUDE DE LA REGULATION DE L'EXPRESSION DU GENE HUMAIN hGATA-3
(REGULATION OF THE HUMAN GATA-3 GENE)

GREGOIRE Jean-Marc; ROMEO Paul-Henri, dir

Universite de Paris 07, Paris, France

Univ.: Universite de Paris 07. Paris. FRA Degree: Th. doct.

1998-12; 1998 152 p.

Language: French Summary Language: French; English

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... cellules souches hematopoietiques puis uniquement dans la lignee lymphocytaire T. Dans cette lignee, GATA-3 regulerait l'expression des differentes chaines du recepteur a l'**antigene** et serait impliquee dans la mise en place du phenotype ***Th2***. Cette proteine est egalement un regulateur de l'embryogenese puisque sa perte de fonction entraine un phenotype letal a l'etat homozygote. Nous avons clone...

... la lignee lymphocytaire T et l'analyse de la sequence du promoteur du gene hGATA-3 a montre qu'il etait contenu dans un ilot **CpG**, structure generalement trouvee dans les genes d'expression ubiquitaire. De plus, par transfection stable, nous avons montre que l'unite de transcription hGATA-3 (20kb...

English Descriptors: Regulation(control); Gene expression; Human; Gene;
Transcription factor GATA3; Hematopoietic cell; Embryonic development; T-Lymphocyte; Cell differentiation; Transcription repressor; Kidney; Promoter; Transcription

14/3,K/6 (Item 1 from file: 357)

DIALOG(R)File 357:Derwent Biotech Res.

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0364877 DBR Accession No.: 2005-10581 PATENT

Modifying an immune response for treating hemorrhagic or neuropathologic viral infection by providing a host cell with a thioaptamer that modifies the activity of a DNA-binding protein involved in an immune response - involving vector-mediated gene transfer and expression in host cell for therapy

AUTHOR: GORENSTEIN D G; LUXON B A; HERZOG N; ARONSON J F; BEASLEY D; BARRET A; SHOPE R E; YANG X B

PATENT ASSIGNEE: UNIV TEXAS SYSTEM 2005

PATENT NUMBER: WO 200518537 PATENT DATE: 20050303 WPI ACCESSION NO.: 2005-196216 (200520)

PRIORITY APPLIC. NO.: US 472888 APPLIC. DATE: 20030523

NATIONAL APPLIC. NO.: WO 2004US16246 APPLIC. DATE: 20040520

LANGUAGE: English

...ABSTRACT: INDEPENDENT CLAIMS are also included for the following: (1) a method for shifting the type of helper T cell response; (2) a vaccine comprising an **antigen** and a thioaptamer specific for a DNA-binding protein where at least a portion of at least one nucleotide of the thioaptamer is thio-modified; (3) a composition comprising an adjuvant comprising one or more thioaptamers specific for a protein that modulates an innate immune response and at least one **antigen**; (4) an adjuvant comprising one or more thioaptamers that bind a DNA-binding protein and modulate an immune response; (5) a T cell adjuvant comprising an aptamer specific for a **transcription factor** involved in T cell activation where at least a portion of at least one nucleotide is thiophosphate-modified; (6) a method of treating a hemorrhagic...

...an innate immune response. The immune response is a helper T cell immune response. The modification of the immune response is a shift in a ***Th1*** to ***Th2*** ratio. The immune response is to bacteria, fungus, cancer, self-**antigen**, heterologous **antigen**, retrovirus, hemorrhagic virus or neuropathologic virus. The immune response is in vivo. The thioaptamer modifies antibody production or cytotoxic T cell activation. Modifying an immune response comprises administering to a host a composition comprising an **antigen** and one or more partially thio-modified aptamers specific for a DNA-binding protein. The composition further comprises IL-1, 2, 3, 4, 5, 6...

... CSF), monocyte-macrophage CSF, granulocyte CSF, vascular epithelial growth factor (VEGF), angiogenin, transforming growth factor (TGF-alpha), fibroblast growth factor, angiostatin and/or endostatin. The **antigen** comprises lipid A, phospholipase A2, endotoxins, staphylococcal enterotoxin B, heat shock proteins (HSPs), carbohydrates, Rh factors, DNA, nucleotides, RNA, mRNA, MART, MAGE, BAGE, GAGE, DAGE, mutant p53 and/or tyrosinase. The aptamer stimulates **antigen**-presenting cells consisting of macrophages, dendritic cells or B cells. The aptamer activates an innate immune response. The aptamer activates an innate immune response through...

... patient suspected of being infected with a hemorrhagic virus and providing the patient with a therapeutic amount of a partially thio-modified aptamer specific for **transcription factor** involved in immune cell activation. The hemorrhagic virus comprises a virus comprising Lassa virus, Junin virus, Machupo virus, Guanarito virus, Sabia virus, Argentine hemorrhagic fever...

... patient suspected of being infected with a neuropathologic virus and providing the patient with a therapeutic amount of a partially thio-modified aptamer specific for **transcription factor** involved in immune cell activation. Enhancing vaccine efficacy comprises administering a composition comprising a partially thio-modified aptamer specific for a DNA binding protein and an ***antigen***. The method further comprises a carrier molecule, comprising liposomes, microcapsules and/or microspheres. The immune response is to a cancer, allergic rhinitis, eczema, urticaria, anaphylaxis...

... Waldenstrom's macroglobulinemia, amyloidosis, chronic lymphocytic leukemia or non-Hodgkin's lymphoma. The partially thio-modified aptamer specific for a DNA binding protein and an **antigen** are a vaccine disposed in a vehicle suitable for oral, intramuscular, subcutaneous, intravenous or parenteral administration. Preferred Vaccine: The vaccine comprises an **antigen** and a thioaptamer specific for a DNA-binding protein where at least a portion of at least one nucleotide of the thioaptamer is thio-modified. The vaccine comprises one or more pharmaceutically acceptable salts. The ***antigen*** comprises a virus, a bacterium, a fungus, a cancer, a self-**antigen**, a heterologous **antigen**, a retrovirus, a hemorrhagic virus or a neuropathologic virus. The ***antigen*** comprises a West Nile Virus. The vaccine is lyophilized. The DNA-binding protein comprises AP-1. The vaccine is in a dissolved form. The ***antigen*** comprises a live-attenuated ***antigen***. The ***antigen*** comprises a heat-inactivated ***antigen***. Preferred Composition: The composition comprises an adjuvant comprising one or more thioaptamers specific for a protein that modulates an innate immune response and at least one **antigen**. The composition further comprises a physiologically acceptable aqueous vehicle. The composition is lyophilized. The ***antigen*** is in a particulate or dissolved form. The ***antigen*** comprises a live-attenuated or heat-inactivated ***antigen***. The ***antigen*** comprises a pathogen-associated molecular pattern **antigen**, which

is a ***CpG*** molecule or polysaccharide. The thioaptamer comprises a concatenated aptamer comprising one or more concatenated thioaptamers. The protein that the thioaptamer binds specifically with comprises a...

... RBP-JK, AP-1, NF IL-6, SP-1, GRE or SRE. The thioaptamer comprises nucleic acid sequences for binding specifically to one or more **transcription factors** consisting of NF-KB, RBP-JK, AP-1, NF IL-6, SP-1, GRE or SRE. The thioaptamer comprises one or more of the aptamers...

... immune response comprises an innate or adaptive immune response. The adjuvant further comprises a physiologically acceptable aqueous vehicle and a live-attenuated or heat-inactivated ***antigen***. The thioaptamer binds to downstream nuclear regulatory factors that transduce an intracellular signal from a Toll-Like receptor 2 or 4. **ACTIVITY** - Virucide. No biological...

14/3,K/7 (Item 1 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
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141393958 CA: 141(24)393958s JOURNAL
Impact of modifications of heterocyclic bases in CpG dinucleotides on their immune-modulatory activity
AUTHOR(S): Vollmer, Joerg; Weeratna, Risini D.; Jurk, Marion; Davis, Heather L.; Schetter, Christian; Wuellner, Meike; Wader, Tanja; Liu, Ming; Kritzler, Andrea; Krieg, Arthur M.
LOCATION: Coley Pharmaceutical, Langenfeld, Germany,
JOURNAL: J. Leukocyte Biol. (Journal of Leukocyte Biology) DATE: 2004
VOLUME: 76 NUMBER: 3 PAGES: 585-593 CODEN: JLBIE7 ISSN: 0741-5400
LANGUAGE: English PUBLISHER: Federation of American Societies for Experimental Biology

14/3,K/8 (Item 2 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
(c) 2005 American Chemical Society. All rts. reserv.

141337728 CA: 141(20)337728e PATENT
Microparticles comprising biodegradable polymers with adsorbent surfaces for absorbing tumor antigen, methods of making same, and therapeutic uses thereof
INVENTOR(AUTHOR): O'Hagan, Derek
LOCATION: USA
PATENT: U.S. Pat. Appl. Publ. ; US 20040202680 A1 DATE: 20041014
APPLICATION: US 357303 (20030203) *US PV36316 (19970130) *US PV69749 (19971216) *US 15652 (19980129) *US 124533 (19980729) *US 285855 (19990402) *WO 99US17308 (19990729) *US 581772 (20000615)
PAGES: 20 pp., Cont.-in-part of U.S. Ser. No. 581,772. CODEN: USXXCO
LANGUAGE: English CLASS: 424277100; A61K-009/50A; A61K-009/14B; A61K-009/16B; A61K-039/00B; C07H-021/04B

14/3,K/9 (Item 3 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
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141105241 CA: 141(7)105241n PATENT
Viral antigen encoded by CpG-optimized plasmid vector for immunization against viral infection especially AIDS
INVENTOR(AUTHOR): Kent, Stephen J.; Purcell, Damian F.; Boyle, David B.; Ramsay, Alistair; Thomson, Scott; Ramshaw, Ian A.

LOCATION: Australia
ASSIGNEE: The University of New South Wales
PATENT: PCT International ; WO 200456391 A1 DATE: 20040708
APPLICATION: WO 2003AU1705 (20031219) *AU 20022002953556 (20021220) *AU
20032003905067 (20030917)
PAGES: 280 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: A61K-039/21A;
A61K-039/395B; A61K-039/02B; A61P-031/12B; A61P-031/18B
DESIGNATED COUNTRIES: AE; AG; AL; AM; AT; AU; AZ; BA; BB; BG; BR; BW; BY;
BZ; CA; CH; CN; CO; CR; CU; CZ; DE; DK; DM; DZ; EC; EE; EG; ES; FI; GB; GD;
GE; GH; GM; HR; HU; ID; IL; IN; IS; JP; KE; KG; KP; KR; KZ; LC; LK; LR; LS;
LT; LU; LV; MA; MD; MG; MK; MN; MW; MX; MZ; NI; NO; NZ; OM; PG; PH; PL; PT;
RO; RU; SC; SD; SE; SG; SK; SL; SY; TJ; TM; TN; TR; TT; TZ; UA; UG; US; UZ;
VC; VN; YU; ZA; ZM; ZW DESIGNATED REGIONAL: BW; GH; GM; KE; LS; MW; MZ; SD
; SL; SZ; TZ; UG; ZM; ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM; AT; BE; BG;
CH; CY; CZ; DE; DK; EE; ES; FI; FR; GB; GR; HU; IE; IT; LU; MC; NL; PT; RO;
SE; SI; SK; TR; BF; BJ; CF; CG; CI; CM; GA; GN; GQ; GW; ML; MR; NE; SN; TD;
TG

14/3,K/10 (Item 4 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
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140058003 CA: 140(5)58003d JOURNAL
Antigenic Epitopes Fused to Cationic Peptide Bound to Oligonucleotides
Facilitate Toll-Like Receptor 9-Dependent, but CD4+ T Cell
Help-Independent, Priming of CD8+ T Cells
AUTHOR(S): Schirmbeck, Reinhold; Riedl, Petra; Zurbriggen, Rinaldo;
Akira, Shizuo; Reimann, Joerg
LOCATION: Department of Medical Microbiology and Immunology, University
of Ulm, Ulm, Germany, D-89081
JOURNAL: J. Immunol. (Journal of Immunology) DATE: 2003 VOLUME: 171
NUMBER: 10 PAGES: 5198-5207 CODEN: JOIMA3 ISSN: 0022-1767 LANGUAGE:
English PUBLISHER: American Association of Immunologists

14/3,K/11 (Item 5 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
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138135825 CA: 138(10)135825m PATENT
Therapeutic application of HIV-1 Tat protein
INVENTOR(AUTHOR): Ensoli, Barbara
LOCATION: Italy
ASSIGNEE: Istituto Superiore di Sanita
PATENT: European Pat. Appl. ; EP 1279404 A1 DATE: 20030129
APPLICATION: EP 2001118114 (20010726)
PAGES: 98 pp. CODEN: EPXXDW LANGUAGE: English CLASS: A61K-039/00A;
A61K-039/39B; A61P-035/00B; A61P-031/00B DESIGNATED COUNTRIES: AT; BE; CH;
DE; DK; ES; FR; GB; GR; IT; LI; LU; NL; SE; MC; PT; IE; SI; LT; LV; FI; RO;
MK; CY; AL; TR

14/3,K/12 (Item 6 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
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137336724 CA: 137(23)336724f PATENT
Vaccine comprising human immunodeficiency virus antigens and human
papillomavirus and/or herpes simplex virus antigens
INVENTOR(AUTHOR): Debrus, Serge; Mathy, Nathalie Louise; Voss, Gerald
LOCATION: Belg.
ASSIGNEE: Glaxosmithkline Biologicals S.A.

PATENT: PCT International ; WO 200287614 A2 DATE: 20021107
APPLICATION: WO 2002EP4966 (20020425) *GB 200110431 (20010427)
PAGES: 34 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: A61K-039/295A;
A61P-031/18B DESIGNATED COUNTRIES: AE; AG; AL; AM; AT; AU; AZ; BA; BB; BG;
BR; BY; BZ; CA; CH; CN; CO; CR; CU; CZ; DE; DK; DM; DZ; EC; EE; ES; FI; GB;
GD; GE; GH; GM; HR; HU; ID; IL; IN; IS; JP; KE; KG; KP; KR; KZ; LC; LK; LR;
LS; LT; LU; LV; MA; MD; MG; MK; MN; MW; MX; MZ; NO; NZ; OM; PH; PL; PT; RO;
RU; SD; SE; SG; SI; SK; SL; TJ; TM; TN; TR; TT; TZ; UA; UG; US; UZ; VN; YU;
ZA; ZM; ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM DESIGNATED REGIONAL: GH; GM
; KE; LS; MW; MZ; SD; SL; SZ; TZ; UG; ZM; ZW; AT; BE; CH; CY; DE; DK; ES;
FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; TR; BF; BJ; CF; CG; CI; CM; GA;
GN; GQ; GW; ML; MR; NE; SN; TD; TG

14/3,K/13 (Item 7 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
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136400308 CA: 136(26)400308g JOURNAL
Role of mitogen-activated protein kinases in CpG DNA-mediated IL-10 and
IL-12 production: central role of extracellular signal-regulated kinase in
the negative feedback loop of the CpG DNA-mediated Th1 response
AUTHOR(S): Yi, Ae-Kyung; Yoon, Jae-Geun; Yeo, Seon-Ju; Hong, Soon-Cheol;
English, B. Keith; Krieg, Arthur M.
LOCATION: Children's Foundation Research Center, Le Bonheur Children's
Hospital, University of Tennessee Health Science Center, Memphis, TN, 38103
, USA
JOURNAL: J. Immunol. DATE: 2002 VOLUME: 168 NUMBER: 9 PAGES:
4711-4720 CODEN: JOIMA3 ISSN: 0022-1767 LANGUAGE: English PUBLISHER:
American Association of Immunologists

14/3,K/14 (Item 8 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
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136261808 CA: 136(17)261808e PATENT
New Toll-like receptors of mouse and their use in high throughput
screening for CpG methylated DNA for use as immunomodulator
INVENTOR(AUTHOR): Bauer, Stefan; Lipford, Grayson; Wagner, Hermann
LOCATION: Germany,
ASSIGNEE: Coley Pharmaceutical G.m.b.H.
PATENT: PCT International ; WO 200222809 A2 DATE: 20020321
APPLICATION: WO 2001US29229 (20010917) *US PV233035 (20000915) *US
PV263657 (20010123) *US PV291726 (20010517) *US PV300210 (20010622)
PAGES: 194 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: C12N-015/00A
DESIGNATED COUNTRIES: AE; AG; AL; AM; AT; AU; AZ; BA; BB; BG; BR; BY; BZ;
CA; CH; CN; CO; CR; CU; CZ; DE; DK; DM; DZ; EC; EE; ES; FI; GB; GD; GE; GH;
GM; HR; HU; ID; IL; IN; IS; JP; KE; KG; KP; KR; KZ; LC; LK; LR; LS; LT; LU;
LV; MA; MD; MG; MK; MN; MW; MX; MZ; NO; NZ; PH; PL; PT; RO; RU; SD; SE; SG;
SI; SK; SL; TJ; TM; TR; TT; TZ; UA; UG; US; UZ; VN; YU; ZA; ZW; AM; AZ; BY;
KG; KZ; MD; RU; TJ; TM DESIGNATED REGIONAL: GH; GM; KE; LS; MW; MZ; SD; SL
; SZ; TZ; UG; ZW; AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU;
MC; NL; PT; SE; TR; BF; BJ; CF; CG; CI; CM; GA; GN; GQ; GW; ML; MR; NE; SN;
TD; TG

14/3,K/15 (Item 9 from file: 399)
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135166007 CA: 135(12)166007p PATENT
Pharmaceutical composition for immunomodulation and preparation of

vaccines comprising an antigen and an immunogenic oligodeoxynucleotide and a polycationic polymer as adjuvants

INVENTOR(AUTHOR): Lingnau, Karen; Mattner, Frank; Schmidt, Walter; Birnstiel, Max; Buschle, Michael

LOCATION: Austria

ASSIGNEE: Cistem Biotechnologies Gmbh

PATENT: PCT International ; WO 200154720 A1 DATE: 20010802

APPLICATION: WO 2001EP87 (20010105) *AT 2000129 (20000128)

PAGES: 39 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: A61K-039/39; A61K-039/002; A61K-039/02; A61K-039/12; A61P-035/00; A61P-037/00; A61K-031/722; A61K-031/7125; C07K-014/34; C07K-014/155

DESIGNATED COUNTRIES: AE; AG; AL; AM; AT; AU; AZ; BA; BB; BG; BR; BY; BZ; CA; CH; CN; CR; CU; CZ; DE; DK; DM; DZ; EE; ES; FI; GB; GD; GE; GH; GM; HR; HU; ID; IL; IN; IS; JP; KE; KG; KP; KR; KZ; LC; LK; LR; LS; LT; LU; LV; MA; MD; MG; MK; MN; MW; MX; MZ; NO; NZ; PL; PT; RO; RU; SD; SE; SG; SI; SK; SL; TJ; TM; TR; TT; TZ; UA; UG; US; UZ; VN; YU; ZA; ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM DESIGNATED REGIONAL: GH; GM; KE; LS; MW; MZ; SD; SL; SZ; TZ; UG; ZW; AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; TR; BF; BJ; CF; CG; CI; CM; GA; GN; GW; ML; MR; NE; SN; TD; TG

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Advances in Immunology: Allergy and Allergic Diseases (First of Two Parts)
(Review Articles)

Kay, A.B.

The New England Journal of Medicine

Jan 4, 2001; 344 (1),pp 30-37

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TEXT

...vitro their T cells respond to the allergen with a moderate degree of proliferation and the production of interferon-(gamma) by type 1 helper T (***Th1***) cells. (Ref. 5-7) Persons with atopy, by contrast, have an exaggerated response characterized by the production of allergen-specific IgE antibodies; they have elevated...

...common aeroallergens on skin-prick tests. T cells from their blood respond to allergens in vitro by inducing cytokines produced by type 2 helper T (***Th2***) cells (i.e., interleukin-4, 5, and 13), (Ref. 5,7) rather than cytokines produced by Th1 cells (interferon-(gamma) and interleukin-2). There are many exceptions to this rule, but the immunopathological hallmark of allergic disease is the infiltration of affected tissue by ***Th2*** cells. (Ref. 8-10...

...fetus are primed by common environmental allergens that cross the placenta. As a result, the immune response of virtually all newborn infants is dominated by ***Th2*** cells. (Ref. 11) It has been proposed that during subsequent development the normal (i.e., nonatopic) infant's immune system shifts in favor of a Th1-mediated response to inhaled allergens (a process termed ``immune deviation''), (Ref. 12) whereas in the potentially atopic infant there is a further increase in Th2 cells that were primed in utero. Microbes are probably the chief stimuli of protective ***Th1*** -mediated immunity. Macrophages that engulf microbes secrete interleukin-12, which induces Th1 cells and natural killer cells to produce interferon-(gamma), thereby shifting the immune system into an ``allergy-protective'' ***Th1*** -mediated response. Other factors may also

influence whether **Th1** or **Th2** cells dominate the response, including the amount of allergen, the duration of exposure to the allergen, and the avidity of allergen-specific interactions between T cells and

*****antigen***** -presenting cells (Ref. 13,14) (Fig. 1).|*Figure 1.-Immunologic and Cellular Factors Regulating the Expression of *****Th1***** and *****Th2***** Cells. Whether the immune response is dominated by *****Th1***** or **Th2** cells is dependent on interleukin-12 and interleukin-4, respectively, as well as on the avidity of interactions between T cells and **antigen**-presenting cells and the amount of allergen to which the immune system is exposed (*****antigen*****). (Ref. 13,14) In addition, the presence of cytidine-phosphate-guanosine (**CpG**) repeats derived from bacteria favors the **Th1** phenotype, whereas the presence of **transcription factors** such as GATA-3 favors the **Th2** phenotype, (Ref. 15) as does the presence of c-maf and prostaglandin E(sub 2) (PGE(sub 2)). Nitric oxide favors the expression of *****Th2***** cells by being less inhibitory to **Th2** cells than **Th1** cells, whereas in humans interleukin-10 and transforming growth factor (beta) (TGF-(beta)) generally dampen the responses of both types of cells. Interferon-(gamma) (IFN-(gamma)) inhibits **Th2**-mediated responses; both interleukin-12 and interleukin-18 release interferon-(gamma) from T cells. Interleukin-4 inhibits the expression of **Th1** cells and promotes **Th2**-mediated responses. Green arrows indicate stimulatory effects, and red arrows inhibitory effects, of the cytokines *****FIGURE OMITTED*****.

...a Western lifestyle accounts for the increases in prevalence. Perhaps in Western countries the developing immune system is deprived of the microbial antigens that stimulate **Th1** cells, because the environment is relatively clean and the use of antibiotics for minor illnesses in early life is widespread. (Ref. 18...

...in populations exposed to *Helicobacter pylori*, *Toxoplasma gondii*, and hepatitis A virus. By producing an environment rich in interleukin-12, these microbes could drive a *****Th1***** -mediated response. This mechanism may explain why in Europe and Africa, farming or living in a rural community, which increases the likelihood of exposure to...

...Other factors that may favor the *****Th2***** phenotype in infants include diet and being born when pollen counts are high. (Ref. 22) Furthermore, atopic allergic diseases are less common in younger children...

...tobacco smoke, and air pollutants. (Ref. 27) These factors, alone or in combination, may alter immunoregulatory mechanisms at mucosal surfaces in ways that promote a *****Th2***** -mediated allergic inflammatory response (Fig. 2).|*Figure 2.-Factors Influencing the Development of Atopy and Allergic Inflammation Mediated by *****Th2***** Cells (Atopic Allergic Disease). The induction of atopy is dependent on interactions between genes and the environment. The induction of atopic allergic disease may require...the gene for the epsilon class of the constant region (C(sub (epsilon))) of the immunoglobulin heavy chain. The production of IgE also requires two **transcription factors**, nuclear factor (kappa)B and STAT-6; the former pathway involves the costimulatory molecules CD40 and the CD40 ligand (CD154), and the latter is activated when interleukin... Allergens, including the products of some infectious microorganisms (e.g., *Aspergillus fumigatus*) and helminthic parasites, evoke **Th2**-mediated responses that are characterized by high serum levels of IgE, whereas other bacterial **antigens** (such as those associated with *Listeria monocytogenes* and *Mycobacterium tuberculosis*) elicit a **Th1**-mediated response that is dominated by cellular immunity (the appearance of cytotoxic T cells and delayed hypersensitivity). In this latter class of organisms, the DNA contains repeating sequences of cytosine and guanosine nucleosides called *****CpG***** repeats. These *****CpG***** repeats can bind to receptors on **antigen**-presenting cells and trigger the release of interleukin-12. This cytokine, which is produced almost exclusively by

antigen-presenting cells, drives and maintains the **Th1**-mediated response. Furthermore, the interferon-(gamma) produced by activated *****Th1***** cells (Ref. 39) and interleukin-18, produced by macrophages, (Ref. 39) join forces to suppress the production of IgE antibodies. (Ref. 40) Therefore, at least...

...interferon-(gamma), interleukin-12, and interleukin-18, either alone or in combination, have therapeutic potential for inhibiting the synthesis of IgE. Furthermore (as discussed below), *****CpG***** repeats may redirect allergens to produce a **Th1**-mediated, rather than a **Th2**-mediated, immune response...initiating and controlling allergic inflammation. Dendritic cells and cutaneous Langerhans' cells are particularly important in asthma and atopic eczema, respectively. They present antigen to CD4+ **Th2** cells in an MHC class II-restricted fashion. Overproduction of the granulocyte-macrophage colony-stimulating factor in the airway mucosa of patients with asthma enhances...

...of macrophages. (Ref. 12) Alveolar macrophages obtained from patients with asthma by bronchoalveolar lavage present allergen to CD4+ T cells and stimulate the production of *****Th2***** -type cytokines, (Ref. 49) whereas alveolar macrophages from control subjects do not...

... *****Th2***** -type cytokines such as interleukin-4, 5, 9, and 13 influence a wide range of events associated with chronic allergic inflammation. Interleukin-4 and interleukin...

...since they produce fibrogenic growth factors and matrix metalloproteinase, which remodel airway tissue in asthma. (Ref. 52) |*Table 1.-The Role of Cytokines Produced by *****Th2***** Cells in Chronic Allergic Inflammation *.*****TABLE OMITTED**

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 Cancer immunotherapy with CpG-ODN
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ORIGINAL LANGUAGE TITLE: Immunotherapie des cancers par
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ABSTRACT: Bacterial DNA and synthetic oligodeoxynucleotides containing
CpG motifs (**CpG**-ODN) are the ligands for the Toll-like
 receptor 9 (TLR9), which is expressed by B-lymphocytes and a subset of
 dendritic cells. ***CpG*** -ODN are strong activators of both innate and
 specific immunity, and drive the immune response towards the **Th1**
 phenotype. Given the promising results obtained in several experimental
 models of allergies or infections, **CpG**-ODN are now entering
 clinical trials for these diseases. In cancer, promising approaches
 combined **CpG**-ODN with tumor **antigens**, monoclonal antibodies
 or dendritic cells. When no relevant tumor ***antigen*** is known,
CpG-ODN can be used alone to activate locally the innate immunity
 and trigger a tumor-specific immune response, overcoming the need for the
 identification of a tumoral ***antigen***. Preclinical models have shown
 impressive results and several clinical trials are on-going worldwide in
 melanoma, lymphoma, renal carcinoma, breast cancer and glioblastoma.